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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,362	BLACKSHEAR ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-31,33-41,43-46,49-59 and 61-64* is/are pending in the application.

4a) Of the above claim(s) *2-4,7,14,22-24,28-31,33-41,43-46,49-59 and 61-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6,8-13,15-21 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/14/04;2/14/05;1/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Selected sequence search data*.

DETAILED ACTION

Claims 2-31, 33-41, 43-46, 49-59 and 61-64 are pending in the present application.

Applicant's election of Group II (Claims 5-13, 15-21 and 25-27), drawn to an isolated nucleic acid molecule encoding a RFX4_v3 polypeptide, a vector, a host cell comprising the same and first method for producing a variant polypeptide using the same, in the reply filed on 11/01/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants further elected the following species: (a) SEQ ID NO:8 (corresponding SEQ ID NO:37) as a species of an encoded polypeptide; and (b) SEQ ID NO:11 as a species of a promoter.

The examiner further notes that where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claims 2-4, 7, 14, 22-24, 28-31, 33-41, 43-46 and 49-59 and 61-64 were withdrawn because they are directed to non-elected invention and non-elected species (claim 7).

Accordingly, claims 5-6, 8-13, 15-21 and 25-27 are examined on the merits herein with the above elected species.

Claim Objections

Claims 5 and 25 are objected to because they are dependent on a non-elected claim 2. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 12-13 and 20-21 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

The claims are directed to a host cell transformed with a vector comprising a nucleic acid molecule encoding a substantially purified RFX4_v3 polypeptide of the present invention. Since an embodiment of the claims encompasses a host cell in both *in vitro* and *in vivo*, including a cell present in a human subject or patient receiving the treatment (page 22, lines 3-5 and page 23, lines 25-29), such a cell is integrated or present into the human being and therefore being an inseparable part of the human itself. The scope of the claim, therefore, encompasses a human being, which is a non-statutory subject matter.

The examiner notes that the insertion of the term "An isolated" in front of the term "host cell" would obviate the above rejection.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-6 and 8-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

With respect to the elected invention and elected species (SEQ ID NO:37), the instant claims are drawn to an isolated nucleic acid molecule encoding a purified RFX4_v3 polypeptide, wherein the polypeptide comprises: a) an amino acid sequence at least 70% identical to an amino acid sequence of SEQ ID NO:8; b) a conservative variant of the amino acid sequence of SEQ ID NO:8; c) the amino acid sequence of SEQ ID NO:8, wherein the polypeptide has RFX4_v3 activity, and the N-terminus of the

polypeptide is at least 90% identical to residues 1-14 of SEQ ID NO:8; a vector and a host cell comprising the same isolated nucleic acid molecule.

Apart from the disclosure of full-length novel brain specific variant transcripts of RFX4 having SEQ ID NO:37 (human RFX4_v3), SEQ ID NO:38 (mouse SEQ ID NO:39) and SEQ ID NO:39 (zebra), in which both mouse and human RFX4_v3 transcripts encode identical the first 14 N-terminal amino acid residues while the zebra RFX4_v3 transcript encodes for a similar N terminal amino acid sequence with the substitution of a His by a Leu at residue number 2; the instant specification **fails to describe the essential core structure(s) or element(s) possessed by other isolated nucleic acid molecules as broadly claimed such that the encoded polypeptide has RFX4 v3 activity which is defined as any activity that promotes the development of the brain's ventricular system, the absence of which activity is demonstrated by the development of hydrocephalus (see instant specification on page 11, lines 3-5)**. What exactly is the core structure(s) or element(s) that is responsible for the RFX4_v3 activity that an isolated nucleic acid molecule having at least 70% or 90% identical to SEQ ID NO:37, or a nucleic acid molecule encoding a polypeptide comprising an amino acid sequence at least 70% identical to any amino acid sequence as set forth in SEQ ID NO:8 as long as its N-terminus is at least 90% identical to residues 1-14 of SEQ ID NO:8 should possess? The instant specification merely showed that the development of a graded hydrocephalus in a transgenic mouse is the result of a partial and complete deficiency of its full-length RFX4_v3 transcripts. Furthermore, there is no evidence of record or in the prior art at the effective filing date of the present application that the N-

terminal sequence containing the first 14 amino acid residues of SEQ ID NO:8 is responsible for any activity associated with the development of the brain's ventricular system. Moreover, at about the effective filing date of the present application (4/19/02) the physiological functions of RFX gene products, including alternatively spliced variants of RFX4 such as RFX4_v1 and RFX4_v2, were unknown as evidenced at least by the teachings of Morotomi-Yano et al. (J. Biol. Chem. 277:836-842, 2002; IDS), Blackshear et al. (Development 130:4539-4552, 2003; IDS) and Araki et al. (J. Biol. Chem. 279:10237-10242, 2004). The instant specification also fails to provide **a representative number of species for a broad genus of an isolated nucleic acid molecule encoding a polypeptide having RFX4_v3 activity as broadly claimed**.

Furthermore, please note that it is well known in the art that sequence similarity does not reliably correlate to structural similarity and that structural similarity does not reliably result in similar and identical biological activities. For example, it is well known that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in may instances, albeit not in all cases. In the absence of factual evidence characterizing the structural and functional components of the biomolecule, the effects of these changes are largely unpredictable as to which ones will have a significant effect and which ones will be silent mutations having no effect. Several publications document the unpredictability of the relationship between sequence, structure, and function, although it is acknowledged that certain specific sequences have been found to be conserved in biomolecules having related function following a significant amount of further research. See Attwood (Science, 290:471-473, 2000);

Kyrpides et al. (Mol. Microbiology 32:886-887, 1999); Wells et al. (J. Leukocyte Biology 61:545-550, 1997); and Gerhold et al. (BioEssays 18:973-981, 1996).

The claimed invention as a whole is not adequately described **if the claims require essential or critical elements that are not adequately described in the specification**. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). A skilled artisan cannot fully envision the detailed structure of any essential core structure(s) or element(s) for a representative number of species for a broad genus of an isolated nucleic acid molecule encoding a polypeptide having RFX4_v3 activity as broadly claimed, a vector and a host cell comprising the same as broadly claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is the expression of a mutanized nucleic acid sequence, so that the variant can be screened for a RFX4_v3 activity in order to identify the variant of the RFX4_v3 polypeptide.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15-17, 19-21 and 26-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Venter et al. (US 6,812,339; IDS).

With respect to the elected species, Venter et al disclosed genomic nucleotide sequences, transcript sequences including SEQ ID NO:416, encoded amino acid

sequences that contain single nucleotide polymorphisms (see at least Summary of the Invention; col. 5, line 60 continues to line 25 of col.6; col. 9, line 53 continues to line 62). The nucleotide sequence of SEQ ID NO:416 is 72.3% identical (with 99.3% best local similarity) to the nucleotide sequence of SEQ ID NO:37 of the present invention (see attached sequence searches). Such a nucleotide sequence would hybridize to a polynucleotide comprising nucleotides 1-42 of SEQ ID NO: 37. Furthermore, please also note that the term "RFX4_v3 polypeptide" is defined by the instant specification to include fragments of the RFX4_v3 sequence as well as other domains within the full-length RFX_v3 polypeptide (see at least page 10, lines 28-34 of the instant specification). Venter et al further teach that the disclosed nucleic acid molecules may be double stranded molecules and include both a protein encoding strand (sense strand) as well as a complementary nucleotide sequence comprising a sequence complementary to the protein encoding strand or anti-sense strand (col. 8, lines 1-51). The isolated nucleic acid molecule can be cloned into an expression vector, introduced into a host cell such as a bacterial cell, a yeast cell or a mammalian cell for purifying the encoded variant protein (col. 11, lines 40-50; col. 19, lien 39 continues to line 6 of col. 23).

The teachings of Venter et al meet all the limitation of the instant claims as written. Accordingly, the reference anticipates the instant claims.

Claims 15-17, 19-21 and 26-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Nakayama et al. (WO 02/086071; IDS).

With respect to the elected species, Nakayama et al disclosed isolated nucleic acid molecules, including the nucleic acid molecule of SEQ ID NO:7, expression vectors containing these nucleic acid molecules and host cells transfected with these nucleic acid molecules (see at least the Abstract; Summary of the Invention; Figures 3-4). The nucleotide sequence of SEQ ID NO:7 is 82.6% identical (with 99.7% best local similarity) to the nucleotide sequence of SEQ ID NO:37 of the present invention (see attached sequence searches). Such a nucleotide sequence would hybridize to a polynucleotide comprising nucleotides 1-42 of SEQ ID NO: 37. Furthermore, please also note that the term "RFX4_v3 polypeptide" is defined by the instant specification to include fragments of the RFX4_v3 sequence as well as other domains within the full-length RFX_v3 polypeptide (see at least page 10, lines 28-34 of the instant specification). Nakayama et al further teach that the disclosed that the nucleic acid molecules include both a protein encoding strand (sense strand) as well as a complementary nucleotide sequence comprising a sequence complementary to the protein encoding strand or anti-sense strand and their fragments thereof (page 8, lines 8-23). A host cell includes a prokaryotic cell, a yeast cell or a mammalian cell (page 48, lines 18-26).

The teachings of Nakayama et al meet all the limitation of the instant claims as written. Accordingly, the reference anticipates the instant claims.

Claims 5, 15-18 and 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffin et al. (Genes, Chromosomes & Cancer 4:153-157, 1992) as evidenced by Blackshear et al. (Development 130(19):4539-4552, 2003; IDS)

Griffin et al disclosed isolated chromosomes in the form of a karyotype obtained from two human patients having small lymphocytic lymphoma with extranodal involvement (see at least the abstract and Figure 1). The karyotype of human patients in Figure 1 showed intact and isolated human chromosomes #12. Such isolated human chromosomes #4 (an isolated nucleic acid molecule containing both sense and anti-sense strand) would comprise a nucleic acid sequence encoding the RFX4_v3 polypeptide comprising SEQ ID NO:8 as evidenced by the teachings of Blackshear et al., whose gene is located on chromosome 12 (see particularly page 4542, second column, last paragraph continues to first column).

Accordingly, the teachings of Griffin et al. meet the limitation of the instant claims as broadly written, and thus the reference anticipates the instant claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN PH.D.
PRIMARY EXAMINER